PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 646	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/DK2005/000203	International filing date *(day/month/year)* 23.03.2005	Priority date *(day/month/year)* 02.04.2004
International Patent Classification (IPC) or national classification and IPC INV. C07C401/00		
Applicant LEO PHARMA A/S		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 23 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 39 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.12.2005	01.08.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Watchorn, P Telephone No. +31 70 340-2207

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2005/000203

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-46 as originally filed

   Claims, Numbers

   1-44 received on 30.12.2005 with letter of 19.12.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 28,29,34,35,36,40,41 (in full) 42 (in part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☒ no international search report has been established for the said claims Nos. 28,29,31,34,35,36,40,41 (in full) 42 (in part)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☒ neither restricted the claims nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-27,30-33,37-39,43 (in full) 42 (in part) .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25,30,31,33,37-39,42,43,44
	No:	Claims	26,27,32
Inventive step (IS)	Yes:	Claims	1-25,30,43,44
	No:	Claims	26,27,31-33,37-39,42
Industrial applicability (IA)	Yes:	Claims	1-27,30-33,37-39,42,43
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

IV - Unity of invention (Rule 13 PCT)

The separate inventions/groups of inventions are:

1 - Claims 1-25,30,43,44 (in full)

Method of alkylating vitamin D -20-aldehydes to produce 24-keto-26,27-cyclo Vitamin D derivatives, using phosphonate-diester-ketone derivatives (of formula VII) and reagents therefor of formula VII.

2 - Claims 26,27,32 (in full) 42 (in part)

Intermediates of formulae IIIb and Vb and the use thereof in the production of calcipotriol

3 - Claims 28,34 (in full), 42 (in part)

Intermediates of formulae XIIIa and XIVa and the use thereof in the production of calcipotriol

4 - Claims 29,35 (in full), 42 (in part)

Intermediates of formulae XIIIb and XIVb and the use thereof in the production of calcipotriol

5 - Claims 31 (in full) 42 (in part)

Intermediates of formula IIIa and the use thereof in the production of calcipotriol

6 - Claims 33 (in full), 42 (in part)

Intermediates of formulae VIa and VIb and the use thereof in the production of calcipotriol

7 - Claims 36,41 (in full) 42 (in part)

Intermediates of formulae Xva, Xvb, XVIa and XVIb and the use thereof in the production of calcipotriol

8 - Claims 37-39 (in full) 42 (in part)

Intermediates of formulae XX, XXIa and XXII and the use thereof in the production of calcipotriol

9 - Claims 40 (in full) 42 (in part)

Intermediates of formula XXIIIb and the use thereof in the production of calcipotriol

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The most relevant state of the art with regard to the unity of the presently claimed subject matter consists of the following document:

D1 = Tetrahedron, Vol 43(20) pp 4609-4619 (1987)

1) The problem to be solved by the presently claimed subject matter as a whole is the provision of means (processes and intermediates) for the production of the known compound calcipotriol (see page 1, paragraph 1 of the description). This problem is solved in the present application in the processes of claims 1-25, and 44 by the reaction of a Vitamin D-C-20-aldehyde (or a precursor thereof with an aldehyde group in the position corresponding to position 20 of the Vitamin D final product) with a phosphonate ester compound of formula (VII) (see claim 30). This problem is also solved by the provision of the various other intermediate compounds of claims 26-29 and 31-41.

2) It is however, noted that it is the use of the reagent of formula VII (of claim 30) in the process of claims 1-25, 43 and 44 which distinguishes the claimed processes over the corresponding process of the closest state of the art (see D1, page 4612, paragraph 1, where a different triphenylphosphine reagent is used). However, the use of this reagent (VII) does not manifest itself in any of the other intermediates of claims 26-29 and 31-41

because it introduces exactly the same chemical group onto position 20 of the Vitamin D structure as is introduced by the triphenylphosphine reagent in D1 (see D1, page 4612, paragraph 1). Only the phosphonate ester reagent itself of formula (VII) (see claim 30) can be considered to share a special technical feature with the process of claims 1-25,43,44 since its use constitutes the novel feature of the processes of claims 1-25, 43 and 44.

3) Consequently, it can be seen that the intermediates of claims 26-29, 31-41 and the uses thereof in the production of calcipotriol (claim 44) do not share any special technical feature within the meaning of Rule 13.2 PCT with the processes of claims 1-25, 43 and 44 which distinguishes the subject matter of the claims as a whole over the closest state of the art (D1) and since the existence of such a special technical feature is, according to Rule 13.2 PCT, an absolute pre-requisite for unity to be established, the claimed subject matter lacks unity of invention a posteriori betrween the intermediates of claims 26-29,31-41 and their uses in the production of calcipotriol (claim 42) and the processes of claims 1-25, 43, 44 according to Rule 13.1 PCT.

4) It is further noted that the intermediates of claims 26-29, 31-41 appear in various process variants (for the production of calcipotriol) according to claims 10-17. These process variants are as follows (C = calcipotriol):

*IIIb->*Vb->Xa->C [first step = claim 3, whole process = claim 11]

*Via,b->VIIIa,b->Va->IXa->Xa->C [first step = claim 4, whole process = claim 12]

*IIIa->Va->IXa-Xa->C [whole process = claim 10]

*Via,b->VIIIa,b->XIaa,ab,ba,bb->IXa->Xa->C [first step = claim 4, whole process = claim 13]

*XIIIa->*XIVa-Va->IXa->Xa->C [first step = claim 5, whole process = claim 14]

*XIIIb->*XIVb->*XIVa-Va->IXa->Xa->C [first step = claim 6, whole process = claim 15]

*Xva,b->*XVIa,b->*XIVa-Va->IXa->Xa->C [first step = claim 7, whole process = claim 16]

IXX->*XX->*XXIa->*XXII->XXIV->C [first step = claim 8, whole process = claim 17]

All intermediates marked * are claimed pre se in the present application.

5) In this regard it is noted that according to PCT Search and Examination Guidelines 10.18(e) and Adminstrative Instructions, Annex B, Part 1(g)(v), there cannot be unity of invention according to Rule 13.1 PCT between an intermediate and the final product where that intermediate is separated from that final product by another intermediate which is not novel. This also has the effect that where the known intermediate is at a process branch point, then there also exists a lack of unity between intermediates in different preceeding branches of the process.

6) In the present case it can be seen that the intermediate of formula Va, is known from D1 (see D1, page 4612, compound 18). Consequently, all claimed intermediates in the above scheme which occur in the synthesis scheme before this known intermediate lack unity of invention both with the final product and consequently, also with other intermediates occuring a processes variants meeting at this branch point (consisting of the known intermediate of formula Va). This causes the intermediates to form the following groups of compounds : (Via and Vib) ; (XIII, XIVa, XIIIb, XIVb, Xva,b and XVIa,b); (IIIa) all of which were involved in process variants which met at known intermediates Va and were then further processed into Calcipotriol. The intermediates of formulae (XIII and XIVa; XIIIb and XIV; Xva,b and XVIa,b) are all also separated respectively in separate branches from the final product by another common intermediate forming a branch point - compound XIVa. However, the intermediates of formula XIVa are also known from D1 (see page 4619, point 17). This compound disclosed in D1 is explicitly disclaimed from the scope of claim 28 (directed to this intermediates XIVa compound per se), however, when this formula appears in the processes of claims 14 and 15, it is defined without any disclaimer and as such the intermediate of formula XIVa as used in the claimed processes is known from D1 This then means that the intermediates separated from the final product via this intermediate also lack unity reasulting in a grouping of intermediates of formulae (Via and Vib) ; (XIIIa and XIVa) ; (XIIIb and XIVb); (IIIa) all of which were processed via Intermediates of formula Va into Calcipotriol and where ; (XIIIa and XIVa) ; (XIIIb and XIVb) ; (Xva,b and XVIa,b) were all processed via different earlier branch points to the common known intermediate XIVa and then subsequently into Calcipotriol.

7) Furthermore, the intermediates of formula Xa are also known from D1 (see page 4614, compounds 27 and 28) and a such all intermediates occuring in the above scheme which occur before this known intermediate (compounds of formulae IIIb and Vb) lack unity of invention with the final products and the other intermediates mentioned above. This results in a further claimed invention consisting of these intermediates, processed via the known intermediate Xa into calcipotriol.

8) Still further, intermediates of formula XXIV are also known from D1 (see D1, page 4614. compounds 27-29 and 4) and a such all intermediates occuring in the above scheme which occur before this known intermediate (compounds of formulae XX, XXIa, XXII and XXIIIb) lack unity of invention with the final products and the other intermediates mentioned above. This results in a further claimed invention consisting of the intermediates, processed via the known intermediate XXIV into calcipotriol. Furthermore, since XXIIIb and (XX, XXIa and XXII) occur in different branch points which meet at the known intermediate XXIV, there is also a lack of unity of invention between the intermediates of formulae XX, XXIa and XXII and those of formula XXXIIIb.

9) Consequently, the subject matter has been divided up based on the process of claims 1-25,43 and 44 and the essential reagent therefor of formula VII (claim 30) and the various groups of intermediates and the uses thereof in the production of calcipotriol (claim 42) as explained above.

In this regard, it is noted that the applicant has only replied to the objections raised in the WO-ISA to one of the searched claimed inventions (claimed invention 1) in his response of 19.12.2005. Consequently, the argumentation relating to the other searched inventions which were subject to the WO-ISA, requires no additional work, since the claims are substantially unaltered (except for a limitation of claim 1 and the removal of the use of compounds of claim 30 from claim 42 and their insertion into new claim 44). This means there is no additional work involved in repeating the existing opinion on the other searched inventions in the present International Preliminary Examination Report and as such no additional examination fees were requested from the applicant for these (Rule 68.1 PCT).

V - Statement according to Rule 43bis.1(b) PCT and Article 35(2) PCT

V.1 - Invention 1

The most relevant state of the art with regard to claimed invention 1 consists of the following document:

D1: CALVERLEY M J: "SYNTHESIS OF MC 903, A BIOLOGICALLY ACTIVE VITAMIN D METABOLITE ANALOGUE" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 43, no. 20, 1987, pages 4609-4619, XP001147723 ISSN: 0040-4020

The following documents are also of relevance in assessing the inventive step of the presently claimed subject matter of claimed invention 1:

D2: STEINMEYER ANDREAS ET AL: "Synthesis and biological activities of a new series of secosteroids: Vitamin D phosphonate hybrids" STEROIDS, vol. 66, no. 3-5, March 2001 (2001-03), pages 257-266, XP002328551 ISSN: 0039-128X

D3: DAUBEN W G ET AL: "THE SYNTHESIS OF 25 OXO-25-PHOSPHAVITAMIN D-3" TETRAHEDRON LETTERS, vol. 30, no. 6, 1989, pages 677-680, XP002328552 ISSN: 0040-4039

D4: M. A. BLANCHETTE ET AL: "HORNER-WADSWORTH-EMMONS REACTIONS: USE OF LITHIUM CHLORIDE AND AN AMINE FOR BASE SENSITIVE COMPOUNDS" TETRAHEDRON LETTERS., vol. 25, no. 21, 1984, pages 2183-2186, XP002328553 NLELSEVIER SCIENCE PUBLISHERS, AMSTERDAM.

D5: RESUL B ET AL: "PHENYL-SUBSTITUTED PROSTAGLANDINS: POTENT AND SELECTIVE ANTIGLAUCOMA AGENTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 36, no. 2, 1993, pages 243-248, XP000673914 ISSN: 0022-2623

V.1.N - Novelty (of claimed invention 1) (Article 33(2) PCT)

10) The subject matter of claimed invention 1 relates to the process of claims 1-25, 43 and 44. This process relates to the alkylation of a Vitamin D-C_{20}-aldehyde (or a precursor thereof with an aldehyde group in the position corresponding to position 20 of the Vitamin

D final product) with a phosphonate ester compound of formula (VII) (see claim 30) to introduce the 24-keto-26,27-cyclo Vitamin D side chain. In this regard it is noted that the process of D1 (see page 4612, paragraph 1) a different reagent, a triphenylphosphine compound, is used to introduce the 24-keto-26,27-cyclo Vitamin D side chain onto the C_{20}-aldehyde intermediate (or corresponding precursor). Consequently, the process of claims 1-25, 43 and claim 42 (in part - in as far as claim 42 relates to the use of intermediates of formula VII in the production of calcipotriol) is novel according to Article 33(2) PCT. Furthermore, the reagent of formula (VII) used in this reaction is not disclosed in D1. Only one of the phosphonate-diester compounds of formula VII (claim 30) is disclosed in the state of the art (formula: cyclopropyl-C(O)-CH_2-P(O)-$(OEt)_2$), however, this compound is not disclosed anywhere in the state of the art in association with the alkylation of Vitamin-D-derivatives and this compound has been disclaimed from claim 30 (where compounds of formula VII are claimed *per se*). Consequently, claim 30 is also novel according to Article 33(2) PCT.

V.1.IS - Inventive Step (of claimed invention 1) (Article 33(3) PCT)

11) The problem to be solved by the presently claimed subject matter of claimed invention 1 is the provision of an improved means for the introduction of the 24-keto-26,27-cyclo Vitamin D side chain onto Vitamin D-C_{20}-aldehyde (or a precursor thereof with an aldehyde group in the position corresponding to position 20 of the Vitamin D final product) - see page 1, paragraph 1 of the description. This improvement manifests itself particularly in the ability to conduct the reaction a temperature lower than that used in the closest state of the art and which does not necessitate the tedious removal of triphenylphosphine oxide (see page 2, paragraph 3 of the description).

The solution to this problem as presented in claims 1-25, 43 and 44 is to use the phosphonate reagents of formula VII. In this regard it is noted that the process disclosed on page 4612, paragraph 1 of D1 differs from the process of claimed invention 1 only in that the reagent used is a triphenylphosphine reagent, rather than the phosphonate reagent used in claimed invention 1. In this regard it is further noted that the use of ß-keto-phosphonate -diesters in the alkylation of aldehydes to produce the corresponding enone - is known from documents D2-D5 (see D2, page 258, scheme 2; D3, page 678, compounds 7 and 8; D4, page 2184, compounds 6-8; D5, page 244, scheme II). The reactions

disclosed in these documents are as follows:

[chemical-group #1]-CH=O + $(alkylO)_2$-P(O)-CH_2-C(O)-[chemical group #2] ----->

[chemical-group #1]-CH=CH-C(O)-[chemical group #2]

In particular in D2 and D3, these reactions involve the reaction of C_{20}-aldehyde Vitamin D compounds (see D2, page 258, scheme 2) or corresponding C/D-ring fragment-C_{20}-aldehydes (see D3, page 678, compounds 7, 8), so more particularly the reaction in D2:

D2: 1α,3ß-$(OTBS)_2$-9,10-seco-pregn-5(E),7(E),10(19)-trien-20-CHO + NaH (base)

MeO_2C-CH_2-P(O)-$(OEt)_2$ --------->

1α,3ß-$(OTBS)_2$-9,10-seco-androst-5(E),7(E),10(19)-trien-17ß-$CH(CH_3)$-CH=CH-C(O)-OMe

12) Consequently, the use of the same types of phosphonate reagents are known for the introduction of 22-en-24-one-containing side chains onto the C_{-20}-aldehyde groups of Vitamin D derivatives. It is also known from D2-D5 that the reaction temperatures can be lower - see D2 where the reaction is conducted at O°C, D4 0-50°C and D5 room temperature. It is however, noted that none of D2-D4 mention that the use of the phosphonate compounds analogous to those of claim 30 result in a by product which is easier to remove that the triphenylphosphine oxide produced as the by-product in the reaction of D1. Consequently, the use of phosphonate reagents of formula VII in the processes of claims 1-25, 43 and 44 for the production of calciptriol or its precursors is an unobvious solution to this problem and is as such inventive according to Article 33(3) PCT. Furthermore, since the intermediates of claim 30 are involved in an inventive overall process, they are themselves also inventive.

V.2 - Invention 2

The most relevant state of the art with regard to claimed invention 2 consists of the following documents:

D6: SOERENSEN, HANNE ET AL: "In vitro metabolism of Calcipotriol (MC 930), a vitamin D analog" BIOCHEMICAL PHARMACOLOGY , 39(2), 391-3 CODEN: BCPCA6; ISSN: 0006-2952, 1990, XP002343619

D7: US-A-5 247 104 (DELUCA ET AL) 21 September 1993 (1993-09-21)

The following document is also of relevance in assessing the inventive step of claimed invention 2:

D8: WO 87/00834 A (LEO PHARMACEUTICAL PRODUCTS LTD. A/S) 12 February 1987 (1987-02-12)

V.2.N - Novelty (of claimed invention 2) (Article 33(2) PCT)

13) Document D6 discloses a process for the production of the compound MC-1046 (this is the compound (5Z,7E)-1α,3ß-dihydroxy-22-dehydro-24-keto-26,27-cyclised-Vitamin D - a compound falling within the scope of formula II - the products of the process of claim 1 according to claimed invention 1 - for the structure see D6, page 392, figure 2). D6 discloses on page 391, column 2, paragraph 3 a process whereby this compound is produced by taking as starting material the corresponding (5E,7E) 1,3-bis-(t-butyl-dimethylsilyloxy) protected derivative, subjecting it to triplet sensitised isomerisation to the (5Z,7E) 1,3-bis-(t-butyl-dimethylsilyloxy) protected derivative of MC1046 and then deprotecting this with HF to produce MC1046. In this regard it is noted, that this isomerisation reaction results in the (5Z,7E) 1,3-bis-(t-butyl-dimethylsilyloxy) protected derivative of MC 1046, which is identical to a compound of claim 26, wherein R_1 and R_2 are both t-butyl-dimethylsilyl. Consequently, the subject matter of claim 26 lacks novelty according to Article 33(2) PCT. Furthermore, the preferred compound of claim 27 is exactly the same as the above mentioned intermediate produced by the isomerisation reaction of D6 and as such the compound of this claim also lacks novelty over D6 according to Article 33(2) PCT.

14) D7 discloses on column 1, lines 39-65 a general formula relating to 1α,3ß-di-protected (5Z,7E)-Vitamin-D-C_{20}-aldehyde derivatives. The examples of compounds of this

formula as specified in D7 are 1α,3ß-bis(t-butyl-dimethylsilyloxy) protected derivatives. In this regard it is noted that this formula of D7 corresponds to the formula of claim 32, wherein R_1 and R_2 both represent hydroxy protecting groups. The specific example of D7 (example 1) is excluded from the scope of claim 32 by means of a proviso which specifies that R_1 and R_2 cannot both simultaeously be t-butyl-dimethylsilyl groups, however, the scope of general formula disclosed in D7 is in no way limited to this possibility and teaches the use of any hydroxy protecting group in positions 1α and 3ß, furthermore, this formula of D7 is narrower and is covered by the scope of formula IIIb of claim 32 as such the disclosure of D7 is not confined to its examples and the general teaching which is not excluded as a whole from claim 32, falls entirely within the scope of formula IIIb of claim 32, which consequently lacks novelty according to Article 33(2) PCT.

15) Claim 42, in as far as it relates to the use of the compounds of claims 26 and 27 in the synthesis of calcipotriol (named MC903 in D6) is differentiated over D6, since in D6, the above mentioned intermediate was not used in the synthesis of calcipotriol, but rather the procedure known from D1 was used (named reference [2] in D6). Consequently, in as far as claim 42 relates to the use of compounds of claims 26 and 27 in the syntesis of calcipotriol it is novel according to Atricle 33(2) PCT. Furthermore, the intermediates disclosed in D7 are not used in the synthesis of calcipotriol and as such this document does not prejudice the use of compounds of formula IIIb in the synthesis of calcipotriol according to claim 42. Consequently, in as far as claim 42 relates to the use of compounds of formule IIIb of claim 32 in the syntesis of calcipotriol it is novel according to Atricle 33(2) PCT.

V.2.IS - Inventive Step (of claimed invention 2) (Article 33(3) PCT)

16) The problem to be solved by the subject matter of claimed invention 2 is the provision of intermediates for the synthesis of caclipotriol. In the present case, since the compounds of claims 26,27 and 32 are not novel (see above), the subject matter of these claims cannot be considered to be inventive according to Article 33(3) PCT.

17) Furthermore, the compounds of claims 26 and 27 as known from D7 are easily transformed into caclipotriol by simply reducing the 24-ketone group followed by deprotection - this is, in any case, taught in D1 - see D1, page 4612, where 24-ketone

compound 17 is reduced to the corresponding 24-OH compound 22, which is then isomerised to the (5Z,7E) isomer and then deprotected to produce caclipotriol (evidently the intermediate isomerisation step can be ommitted, since the compound known from D7 is already in the (5Z,7E) configuration - this is in any case, explicitly stated in D8, page 5, paragraph 2). Consequently, the subject matter of claims 26 and 27 is also an obvious solution to the above mentioned problem and as such also lacks inventive step (based on the disclosure of D1 in combination with D6) according to Article 33(3) PCT as does the use of these compounds in the preparation of calcipotriol according to claim 42.

18) Furthermore, the known compounds of claim 32 (known from D7), can be transformed into those of claims 26 and 27 (and known from D6) by the methods disclosed in document D1 (Wittig reaction) - see D1, page 4612, where the C_{20}-aldehyde compound 15 or 16 is reacted with a Wittig reagent to produce the 22-dehydro-24-ketone compound 22. And since the intermediates of claims 26 and 27 can be transformed into calcipotriol by processes obvious to the skilled person (see point (17) above), the subject matter of claim 32 is also an obvious solution to the above mentioned problem and as such lacks inventive step according to Article 33(3) PCT as does the use of these compounds in the preparation of calcipotriol according to claim 42.

19) In this regard it is noted that the fact that the prior art processes do not use the Emmons-Wadsworth reagents used in claim 1 of the present application is irrelevant, since the use of this reagent does not manifest itself in the structures of any of the intermediates of claims 26,27 or 32 and these intermediates can be transformed by means known or obvious to the skilled person into the final product calcipotriol.

V.5 - Invention 5

The most relevant state of the art with regard to claimed invention 5 consists of the following documents:

D1: CALVERLEY M J: "SYNTHESIS OF MC 903, A BIOLOGICALLY ACTIVE VITAMIN D METABOLITE ANALOGUE" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 43, no. 20, 1987, pages 4609-4619, XP001147723 ISSN: 0040-4020

D8: WO 87/00834 A (LEO PHARMACEUTICAL PRODUCTS LTD. A/S) 12 February 1987 (1987-02-12)

V.5.N - Novelty (of claimed invention 5) (Article 33(2) PCT)

20) Documents D1 (see page 4612, compound 15) and D8 (see page 27, lines 19-28 - preparation 19) both disclose a compound which is:

(5E,7E) - 1α,3ß-bis-(t-butyldimethylsilyloxy)-9,10-seco-pregan-10(19)-ene 20-aldehyde

This compound falls within the scope of formula IIIa of claim 31, but has been removed from the scope of this compound claim by means of a disclaimer which removes compounds where R_1 and R_2 are both t-butyldimethylsilyl protecting groups. Consequently, the subject matter of claim 31 is novel according to Article 33(2) PCT. Furthermore, the use of these novel compounds of claim 31 in the production of calcipotriol according to claim 42 is, by the same token, also novel according to Article 33(2) PCT.

V.5.IS - Inventive Step (of claimed invention 5) (Article 33(3) PCT)

21) The problem to be solved by the subject matter of claimed invention 5 is the provision of intermediates for the synthesis of calcipotriol. In this regard it is noted that the above mentioned compound disclosed in D1 and D8 was used in both cases as an intermediate in the synthesis of the compound calcipotriol. See in particular D1, page 4612, paragraphs 1-2 and page 4616, paragraph 2 and D8, page 27, lines 19-28 (preparation 19), followed by page 29, lines 10-24 (preparation 25) and page 31, lines 9-18 (preparation 29). Consequently, it can be seen that a compound conforming to all of the structural variables of the compounds of formula IIIa of claim 31 has been used to solve the same technical problem in D1 and D8. Furthermore the use of corresponding intermediates with different combinations of protecting groups to those used in D1 and D8 (which is the only distinguishing feature of claim 31) is an obvious step to the skilled person and a such the intermediates of claim 31 are an obvious solution to the above mentioned problem and as such lack inventive step according to Article 33(3) PCT as does the use of these compounds in the preparation of calcipotriol according to claim 42. In this regard, attention

is drawn to the comments made in point (19) above, which are also applicable to the intermediates of claim 31.

V.6 - Invention 6

The most relevant state of the art with regard to claimed invention 6 consists of the following documents:

D1: CALVERLEY M J: "SYNTHESIS OF MC 903, A BIOLOGICALLY ACTIVE VITAMIN D METABOLITE ANALOGUE" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 43, no. 20, 1987, pages 4609-4619, XP001147723 ISSN: 0040-4020

D8: WO 87/00834 A (LEO PHARMACEUTICAL PRODUCTS LTD. A/S) 12 February 1987 (1987-02-12)

V.6.N - Novelty (of claimed invention 6) (Article 33(2) PCT)

22) Documents D1 (see page 4611, compound 14) and D8 (see page 22, line 20 - page 23, line 29 - preparations 2 and 3) both disclose a compound which is the 6,19-SO_2 adduct of the compound:

(5E,7E) - 1α,3ß-bis-(t-butyldimethylsilyloxy)-9,10-seco-pregan-10(19)-ene 20-aldehyde

This compound falls within the scope of formula VI of claim 33, but has been removed from the scope of this compound claim by means of a disclaimer which removes compounds where R_1 and R_2 are both t-butyldimethylsilyl protecting groups. Consequently, the subject matter of claim 33 is novel according to Article 33(2) PCT. Furthermore, the use of these novel compounds of claim 33 in the production of calcipotriol according to claim 42 is, by the same token, also novel according to Article 33(2) PCT.

V.6.IS - Inventive Step (of claimed invention 6) (Article 33(3) PCT)

23) The problem to be solved by the subject matter of claimed invention 6 is the provision

of intermediates for the synthesis of calcipotriol. In this regard it is noted that the above mentioned compound disclosed in D1 and D8 was used in both cases as an intermediate in the synthesis of the compound calcipotriol. See in particular D1, page 4611, paragraph 2, page 4612, paragraphs 1-2 and page 4616, paragraph 2 and D8, page 22, line 20 - page 23, line 29 - preparations 2 and 3, page 24, lines 15-31 (preparation 6), page 27, lines 19-28 (preparation 19), followed by page 29, lines 10-24 (preparation 25) and page 31, lines 9-18 (preparation 29). Consequently, it can be seen that a compound conforming to all of the structural variables of the compounds of formula VI of claim 33 has been used to solve the same technical problem in D1 and D8. Furthermore the use of corresponding intermediates with different combinations of protecting groups to those used in D1 and D8 (which is the only distinguishing feature of claim 33) is an obvious step to the skilled person and a such the intermediates of claim 33 are an obvious solution to the above mentioned problem and as such lack inventive step according to Article 33(3) PCT as does the use of these compounds in the preparation of calcipotriol according to claim 42. In this regard, attention is drawn to the comments made in point (19) above, which are also applicable to the intermediates of claim 33.

V.8 - Invention 8

The most relevant state of the art with regard to claimed invention 8 consists of the following document:

D9: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; OKAMOTO, MASATO ET AL: "Preparation of 1.alpha.,24-dihydroxy-22(E)-dehydrovitamin D3 and its derivatives" retrieved from STN Database accession no. 1997:139652

Document D9 is an abstract of the Japanese language document, D10, which also contains discernible technical information in the form of process schemes:

D10: JP-A-8325226

The following document is also of relevance in assessing the inventive step of the presenlty claimed invention 8:

D1: TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 43, no. 20, 1987, pages 4609-4619, XP001147723 ISSN: 0040-4020

V.8.N - Novelty (of claimed invention 8) (Article 33(2) PCT)

24) Document D9 discloses the following compounds (these are indane derivatives which used as C/D ring fragments in the synthesis of Vitamin D derivatives - the numbering used below to identify these compounds is the same as that used in the Japanese language full text document D10):

(1) 1H-Inden-4-ol, 1-(2-propenyl-1-methyl-3-formyl)-octahydro-7a-methyl, 4-benzoate ester

(2) 1H-Inden-4-ol, 1-(4-cyclopropyl-4-hydroxy-1-methyl-2-butenyl)-octahydro-7a-methyl, 4-benzoate ester

(3) 1H-Inden-4-ol, 1-[4-cyclopropyl-4-[(1,1-dimethylethyl)dimethylsilyloxy]]-1-methyl-2-butenyl)-octahydro-7a-methyl, 4-benzoate ester

(4) 1H-Inden-4-ol, 1-[4-cyclopropyl-4-[(1,1-dimethylethyl)dimethylsilyloxy]]-1-methyl-2-butenyl)-octahydro-7a-methyl

(5) 1H-Inden-4-one, 1-[4-cyclopropyl-4-[(1,1-dimethylethyl)dimethylsilyloxy]]-1-methyl-2-butenyl)-octahydro-7a-methyl, 4-benzoate ester

25) The compounds (2)-(4) all conform to all of the structural features of formula XXIa of claim 38 wherein:

(2) R_5 = Ph-C(O)-, R_6 = H
(3) R_5 = Ph-C(O)-, R_6 = $tBuMe_2Si$
(4) R_5 = H, R_6= $tBuMe_2Si$

However, each of the above combinations of values of R_5 and R_6 is explicitly excluded from the scope of the formula XXIa of claim 38 by means of provisos in this claim.

Consequently, claim 38 is novel according to Article 33(2) PCT.

26) The compound (5) above conforms to all of the structural features of formula XXII of claim 39 wherein R_6 = $tBuMe_2Si$. However, this specific value of R_6 (defined as a protecting group) is explicitly excluded from formula XII of claim 39 by means of a proviso. Consequently, claim 39 is novel according to Article 33(2) PCT.

27) The compound (1) has a C_{17}-side chain of formula CH_3-CH*-CH=CH-CHO, (wherein * denotes the point of attachment to the indane ring system). The corresponding intermediate of formula XX of claim 37 has a side chain of formula: CH_3-CH*-CH=CH-C(O)-cyclopropyl. Consequently, the intermediates of claim 37 are also novel according to Article 33(2) PCT.

V.8.IS - Inventive Step (of claimed invention 8) (Article 33(3) PCT)

28) The problem to be solved by the subject matter of claimed invention 8 is the provision of intermediates for the synthesis of calcipotriol. In this regard it is noted that the above mentioned compounds (1)-(5) disclosed in D1 and D10, were used in both as intermediates in the synthesis of the compound calcipotriol. See in particular the following passages of the Japanese language full text document, D10:

Passage	*conversion/reaction*	
page 5, col 2, para 35	1->2	
page 6, col 1, para 38	2->3	
page 6, col 1, para 41	3->4->5	
page 7, col 1, para 47	5->6	(6 = 4-bromo methylene C/D-ring synthon)
page 7, col 1,2 para 48-50	6+7->8	(7 = A ring synthon, 8 = 1,3-diprotected calcipotriol)
page 8, col 1/2	8->9	(9 = calcipotriol)

Consequently, it can be seen that a compound conforming to all of the structural variables of the compounds of both formulae XXIa of claim 38 and XXII of claim 39 have been used to solve the same technical problem in D9 and D10. Furthermore the use of corresponding

intermediates with different combinations of protecting groups to those used in D9 and D10 (which is the only distinguishing feature of the compounds of claims 38 and 39) is an obvious step to the skilled person and a such the intermediates of claims 38 and 39 are an obvious solution to the above mentioned problem and as such lack inventive step according to Article 33(3) PCT as does the use of these compounds in the preparation of calcipotriol according to claim 42. In this regard, attention is drawn to the comments made in point (19) above, which are also applicable to the intermediates of claims 38 and 39. It is also noted that D9 and D10 achieve the conjugation of the A and C/D ring synthons via a well known 4-halo-methylene reaction, this reaction in D9 and D10 necessaitates the reaction of the 4-ketone compound (compound (5)) with a halomethylenation agent to produce the 4-bromo-methylene-C/D ring synthon of formula (6), which is subsequently reacted with the appropriate A-ring synthon (a straight chain terminal double and triple bond containing analogue of the cyclohexyl A-ring). It is however, well known to the skilled person (see for example D8, page 16) that the 4-ketone compound can alternatively be directly reacted with an A-ring synthon which is a Wittig reagent. The choice of one or the other synthetic route is known to the skilled person (e.g. the halomethylene route from D9 and D10, the Wittig route from D8). Consequently, the fact that the compound (5) is processed to a 4-halomethylene intermediate which is not foreseen in the present application does not cause the claimed intermediate to acquire inventive step, since it is needed in and suitable for both known procedures and also for the Emmons-Wadsworth reaction used in the present application.

29) The C/D-ring synthon intermediates of claim 37 already have a full C_{17}-side chain in place (with a 24-ketone group) and in the present application this 24-ketone group is reduced to the corresponding 24-hydroxy group (present in the final product caclipotriol). D9 and D10 disclose a different synthetic path where the intermediate of formula (1) with the C_{17}-side chain of formula CH_3-CH*-CH=CH-CHO is chain lengthened to produce the intermediate of formula (2) directly which has a C_{17}-side chain of formula CH_3-CH*-CH=CH-CHOH-cyclopropyl. However, in document D1, there is disclosed the same reaction as in the present application (where an intermediate with a 24-ketone group is reduced to produce the corresponding 24-OH group - see D1, page 4612, reaction step (c) where intermediate compound 19 is converted into intermediate compounds 21 and 22 (different 24-OH isomers) by reduction). This reaction scheme in D1 uses intermediates which correspond to those of claim 37 to produce intermediates corresponding to those of

claim 38, which differ only in that the intermediates in question in D1 already have the A ring attached to the C/D-ring fragment (they are already Vitamin D derivatives), whereas the intermediates of claim 37 are C/D-ring synthons (indane derivatives) which lack the A-ring. However, it is evident to the skilled person that the same reaction sequence (production of the 24-ketone side chain and its reduction to the corresponding 24-OH compound) can be equally carried out on the C/D-ring synthon before it is attached to the A-ring (indeed this also means that there are no 1 or 3-OH groups on the A-ring which need to be protected). Consequently, the skilled person would evidently have contemplated the production of the C/D-ring synthons of claim 37 as a solution to the above mentioned problem when combining the teaching of documents D9/D10 and D1. Consequently, the intermediates of formula XX of claim 37 are an obvious solution to the above mentioned problem and as such not inventive according to Article 33(3) PCT.

VIII - Observations according to Rule 43bis.1(b) PCT

30) The compound of claim 27 falls within the scope of the compound claim 26 - consequently, there is no reason for this claim to be formulated as independent - a reference to claim 26 must be inserted into this claim as required by Rule 6.4 PCT. It is noted that the applicant has inserted a reference to claim 2 - it is presumed that this is a typing error and that it was intended to insert a reference to claim 26.

31) Claims 42-44 specify the use of intermediate compounds in the manufacture of calcipotriol. However, none of these claims speficies how the intermediates are to be converted into calcipotriol (these claims do not specify any reagents, reaction sequences, or reaction conditions by which this might be achieved), consequently these claims are not clear according to Article 6 PCT. Furthermore, in as far as these claims generically embrace the execution of processes not disclosed in the application, they are also not supported by the description according to Atricle 6 PCT, nor are they sufficiently disclosed as reqiured by Article 5 PCT.